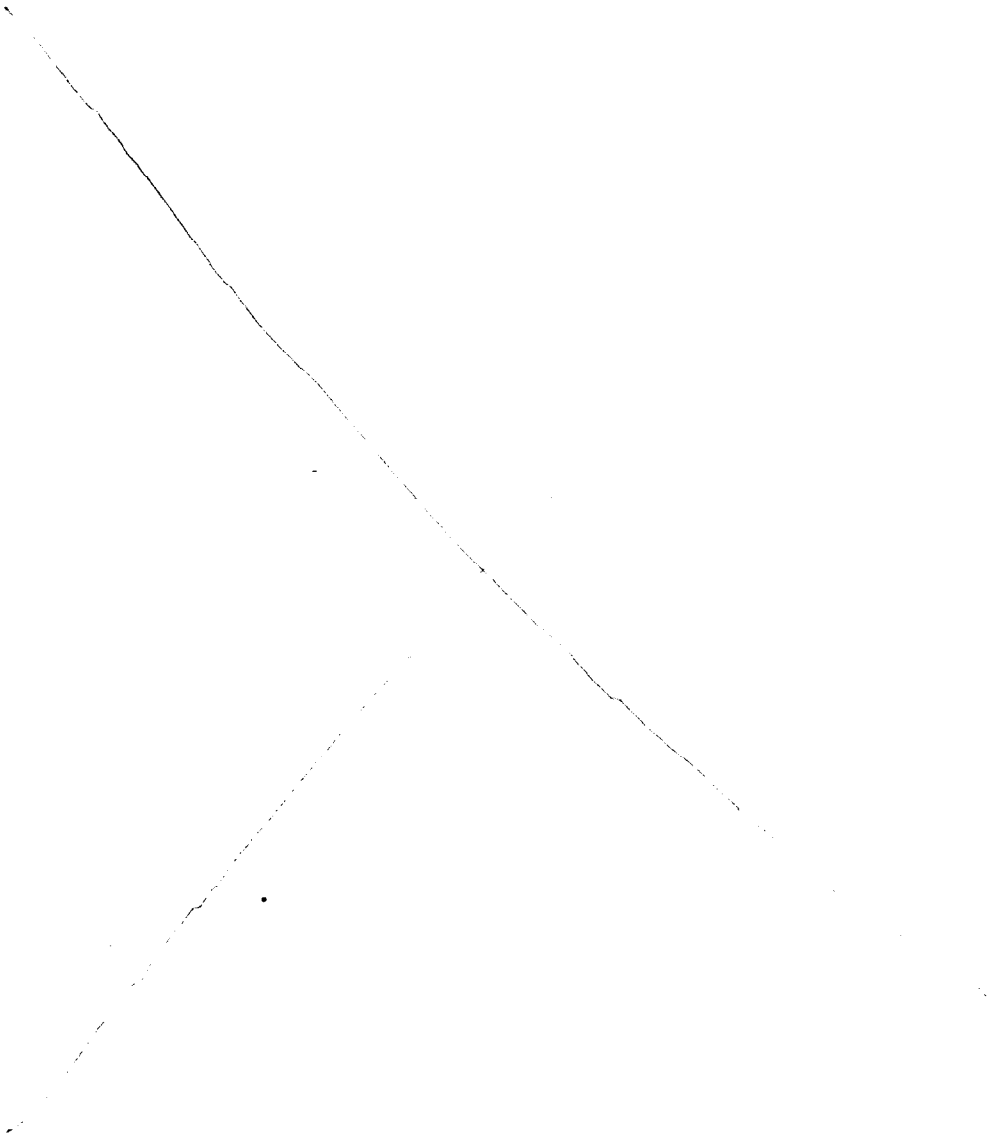


Validations

(from the Process Overview section of the BLA 3.4.2)

Overview Drug Substance

The validation program is described in _____ and applies to areas involved in the manufacturing or evaluation of products prepared under cGMPs (Section 15.8.2). A Validation Committee oversees validation activities and coordinates the function of the following subcommittees: analytical method validation, equipment and facility validation, cleaning validation, computer validation, and process validation. For each validation study a protocol is developed which includes the materials required, the test methods to be used in the study, the critical parameters to be measured, and the acceptance criteria. Following review and approval by the Validation Committee; the protocol is executed, the data is analyzed, and a validation summary report is prepared. The validation report is incorporated into the validation package

which includes the approved protocol, the collected raw data, data analysis, and any other information pertaining to the study. The Validation Committee reviews the package, and documents their approval. The Quality Assurance Department maintains the approved validation package in a secured file storage area. Analytical methods are validated according to ———— which is based on USP 23 recommendations for precision, accuracy, linearity, limit of detection, limit of quantitation, range, specificity, and ruggedness; and the ICH Guidance document on analytical method validation. The impact, if any, on the SOP is included in the validation report.

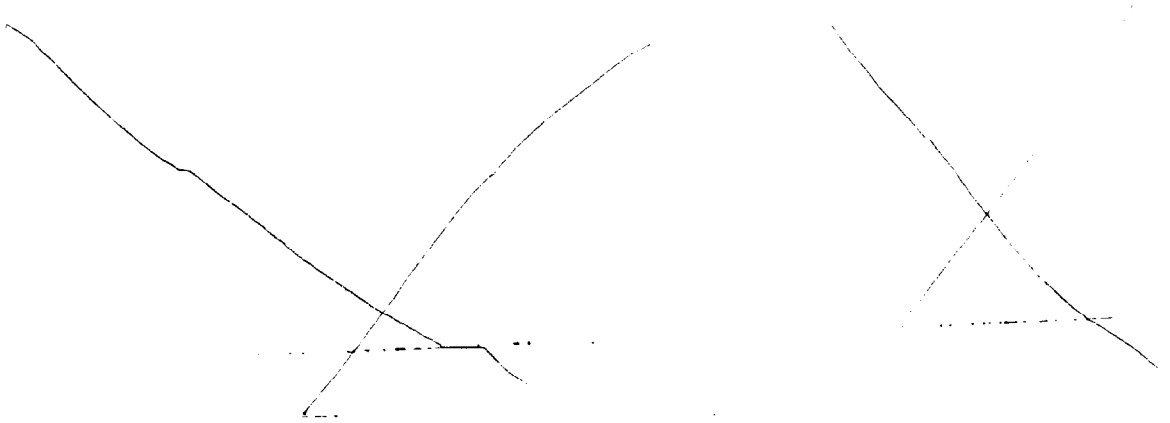
Using this procedure, the test methods used for drug substance and drug product lot release, impurity testing, and stability assessment were validated (Section 6.0). Validations or qualifications (for compendial methods) were also performed on tests supporting release of raw materials (Section 4.2.3.1), cleaning validation studies for process equipment (Section 15.3), and environmental monitoring (Section 15.2.10). The procedure for peptide mapping which is used in comparability analysis (Section 4.2.1.2.3) was also validated.

There are four types of facility or process equipment validation protocols: installation qualification (IQ), operation qualification (OQ), performance qualification (PQ), and process validation (PV). The IQ verifies the correct installation of the equipment and determines the presence of the correct parts, proper calibration or certifications, proper assembly of components; and existence of operational manuals, schematics and other pertinent documentation. The OQ verifies that the equipment operates as quoted by the manufacturer and has the capability of operating within a broad range of parameters including the required process parameter limits. The PQ verifies that the equipment performs consistently within the defined operating parameters when subjected to real-use conditions of operation. Whenever possible, the extremes of the operating range, as well as normal operating limits, are challenged and qualified. Process validation is conducted to mimic conditions that are anticipated to occur during actual manufacture such as scale or timing, and in most cases was executed during the production of the consistency lots.

Critical utilities such as reverse osmosis deionized (RODI) water, water for injection (WFI), clean steam, compressed air, and specialty gases were validated (Section 15.8.2). Validations were also performed on the HVAC, waste treatment, and clean in place (CIP) systems; and support equipment such as the glasswasher, autoclave, depyrogenation oven, refrigerators, and freezers. Validations for major process equipment included biological safety cabinets, horizontal laminar flow hoods, incubators, bioreactors, tanks, filtration systems, buffer preparation systems, chromatography columns, and the chromatography controller (Section 15.8.2). Cleaning validations were included for product contact equipment as part of the performance qualifications. The cell culture and purification operations validations were based on operational and performance specifications (Section 4.2.4.2). Process validation studies consisted of three components summarized in the following reports: Proven Acceptable Range (PAR) Reports, Development Reports, and Consistency Run Validation Reports. Critical operating parameters were selected based on experience from process development and clinical production campaigns. Data collected during clinical production campaigns were used to determine PARs for critical operating parameters. Development studies were performed to determine safe operating windows for critical operating parameters. The PAR and development study data were used to define the critical parameter specifications for the Consistency Run Validations. The cell culture process operations validated are the medium and nutrient feed preparation, the inoculum expansion, the bioreactor operation and the harvest operation. The sterilization of cell culture medium using 0.2 micron filters at each preparation scale ———————— the sterility of the

filtered medium held in storage containers [redacted] and the NS0 cell inactivation by the waste treatment system were also validated (Section 4.2.4.2). Purification process validations included the four chromatography steps, [redacted] treatment, the [redacted] the formulation, and the 0.2 micron bulk filtration.

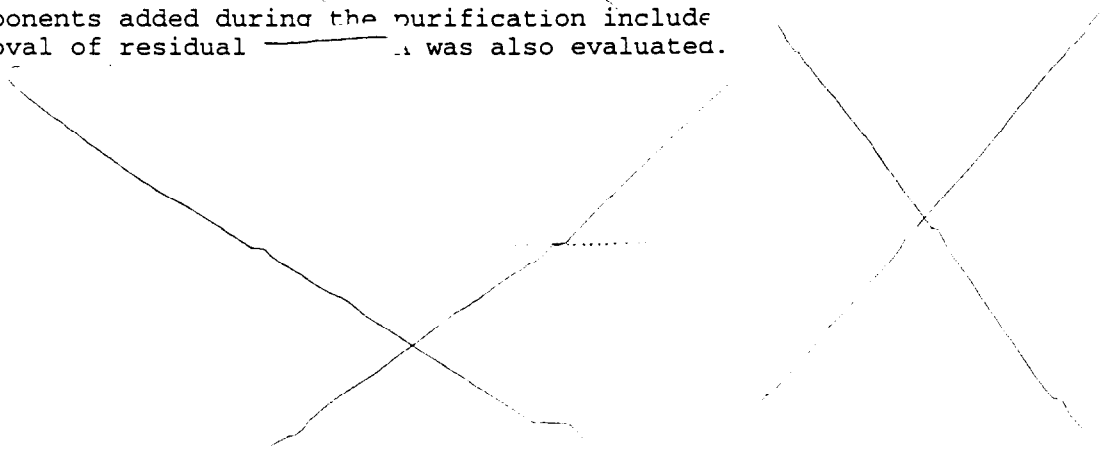
In addition to the validations based on operational and performance specifications, the removal of process impurities by the purification process was also validated (Section 4.2.4.2).

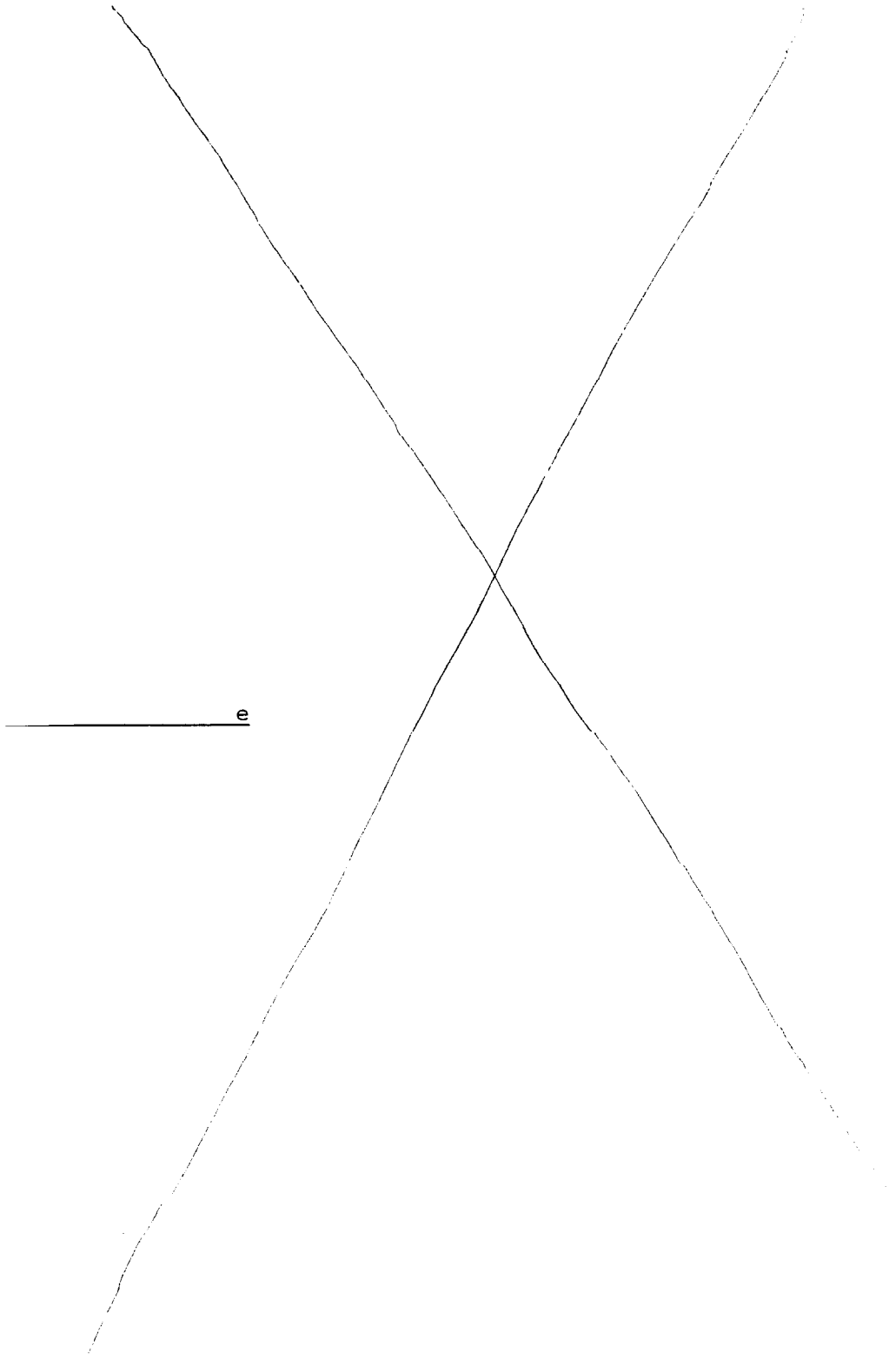


Validations were also performed on computer systems used to control manufacturing process steps (Section 15.7.1); and the tracking of information related to raw materials , environmental monitoring samples, Quality Control (QC) reagents and solutions, QC test samples, the sample inventory, and the inventory of standards and controls (Section 15.7.2).

Impurity Clearance

Process validation studies included in-process analysis to evaluate the removal of cellular and medium components from the product stream. These components include [redacted] . Removal of components added during the purification include [redacted] Removal of residual [redacted] was also evaluated.

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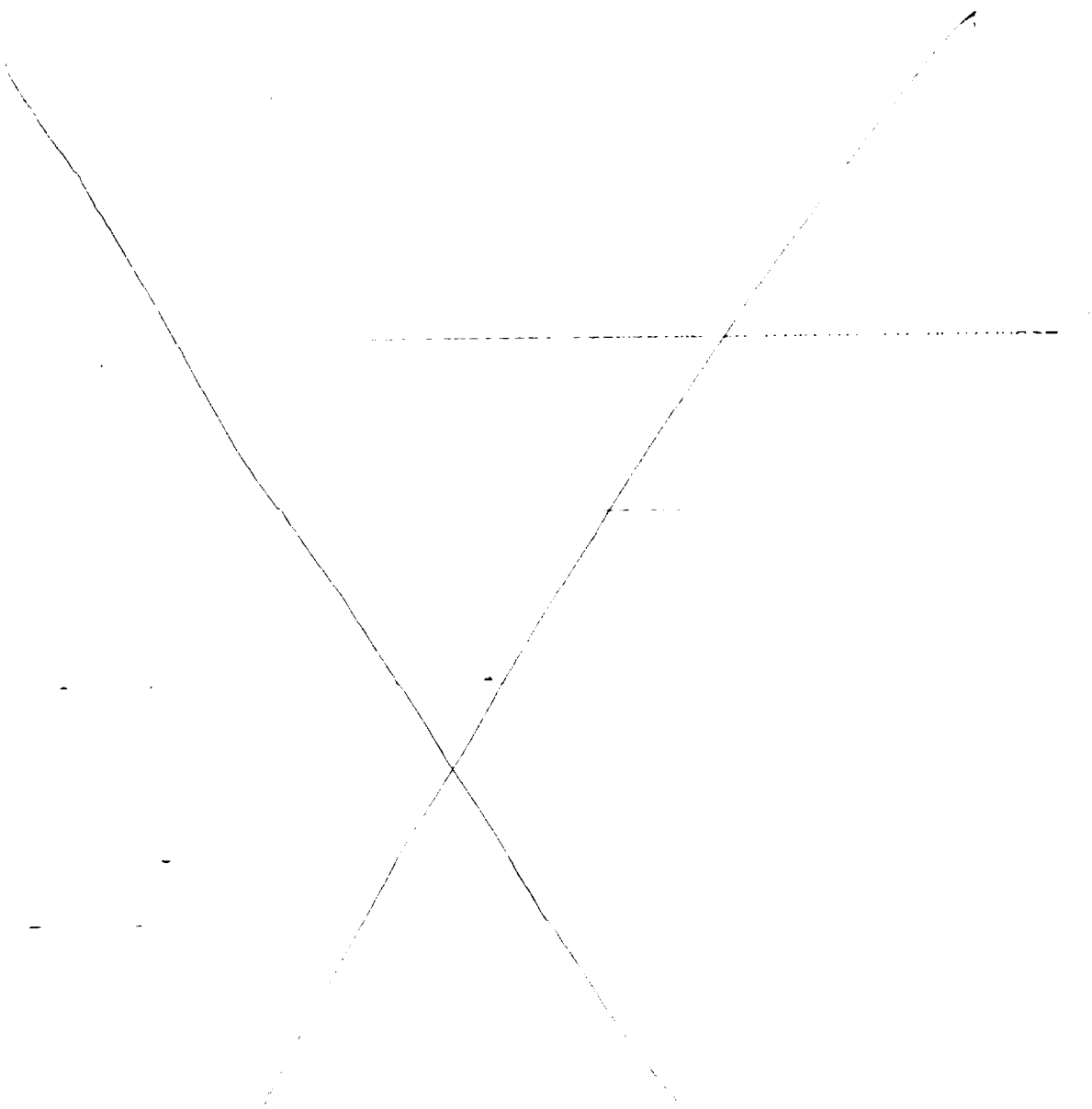
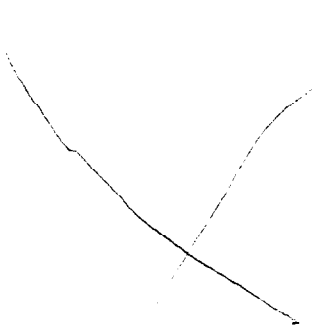




Drug Product

Validations of operations used to prepare the Drug Product are described in Section 15.6. These studies included procedures for washing, siliconization and sterilization of the stoppers; washing and depyrogenation of the vials; cleaning of dedicated product contact filling parts; and cleaning and sterilization of the lyophilizer. The filling, lyophilization, and oversealing procedures, and the Drug Product container/closure integrity (Section 4.3.6) were also validated.

Labeling

(Section 3.4.6)

Labeling of vialed MEDI-493 produced in the [redacted] Product labeling includes the vial label unit carton, and product insert. Artwork for the labeling of 100 mg vials is in Appendix 3.4.6.1.

Later versions have been submitted to the BLA which include the Trade name Synagis

Reference Standard

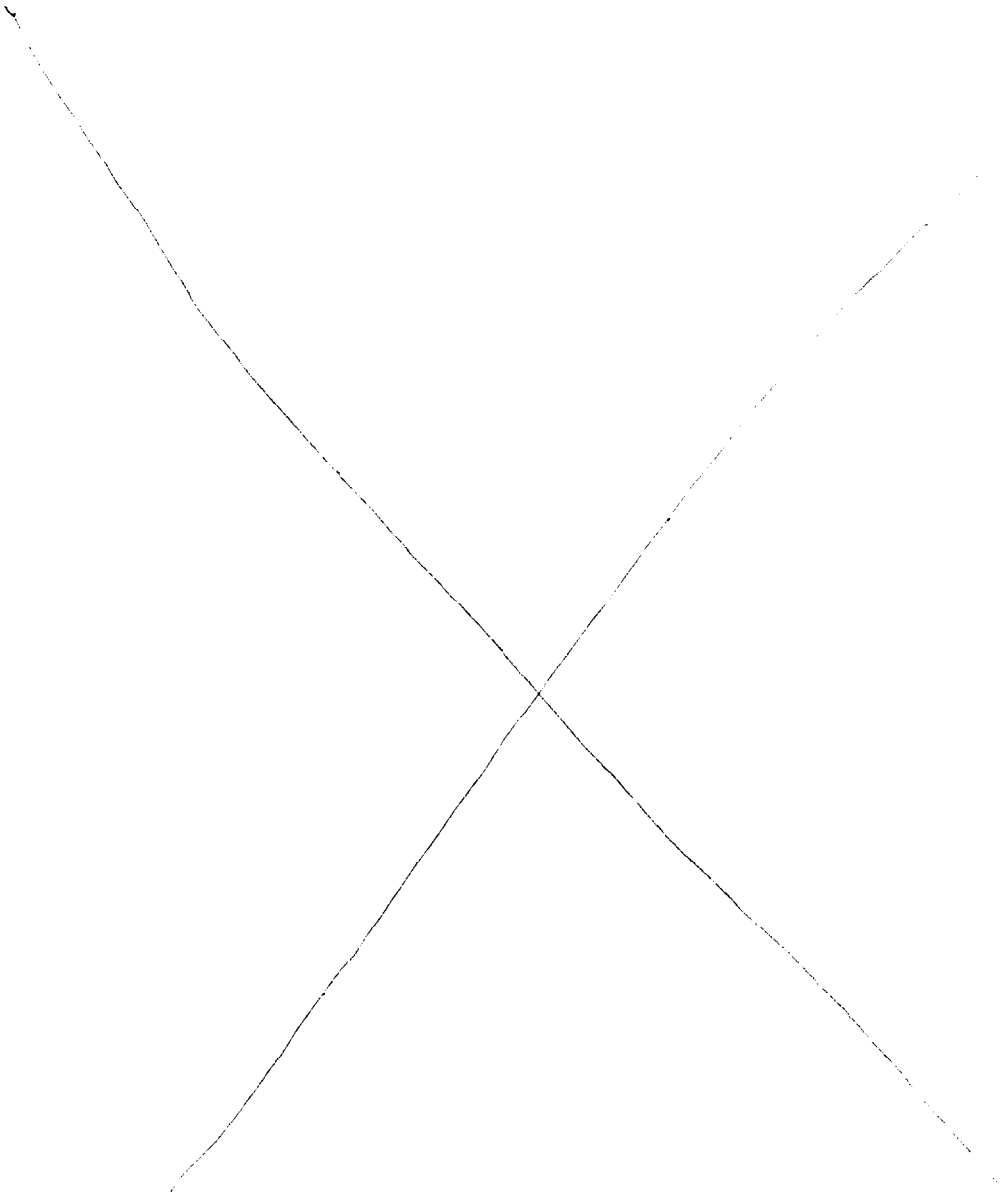
Section 4.2.5 provides a description of the preparation, storage and qualification procedures; and specifications, characterization, and stability data for the Working Reference Standards used during the clinical development of MEDI-493, the production of the MEDI-493 consistency lots, and commercial production.

Working Reference Standards Summary

(from BLA Sections 4.2.5.1-2)

Working Reference Standards are prepared from [redacted] which are stored frozen at [redacted] Liquid and lyophilized reference standard formulations were used during clinical development. Liquid formulation Working Reference Standard vials were thawed, stored at 2-8 °C, and used at the same concentration. Each lyophilized reference standard vial is thawed prior to use, reconstituted in [redacted] of Water for Injection (WFI), diluted to [redacted] with phosphate-buffered saline and stored in [redacted] aliquots at [redacted] for up to [redacted]

Table 4.2.5.2-1 summarizes information on the MEDI-493 Working Reference Standards used to date.



Working Reference Standard Qualification and Characterization

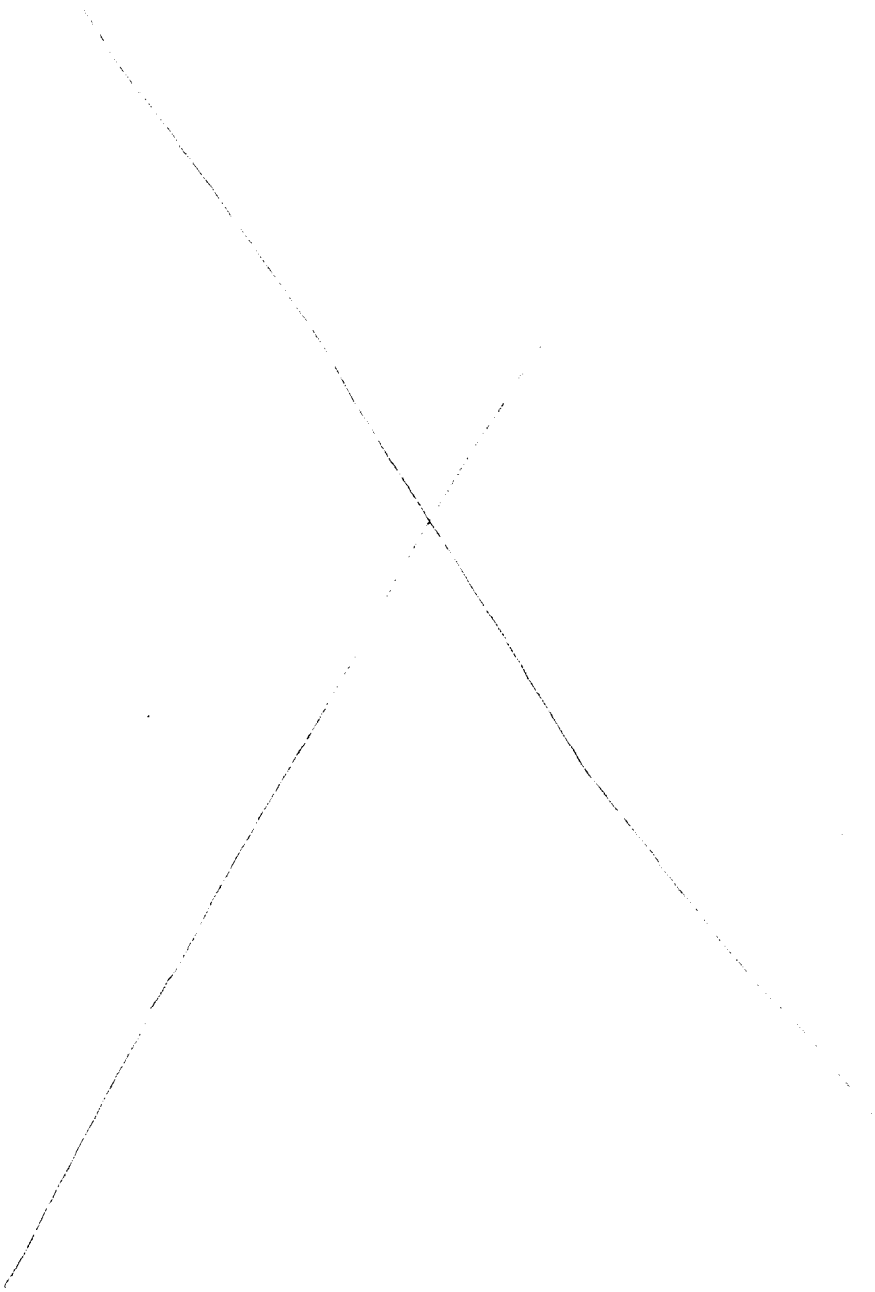
(from BLA Section 4.2.5.3-4)

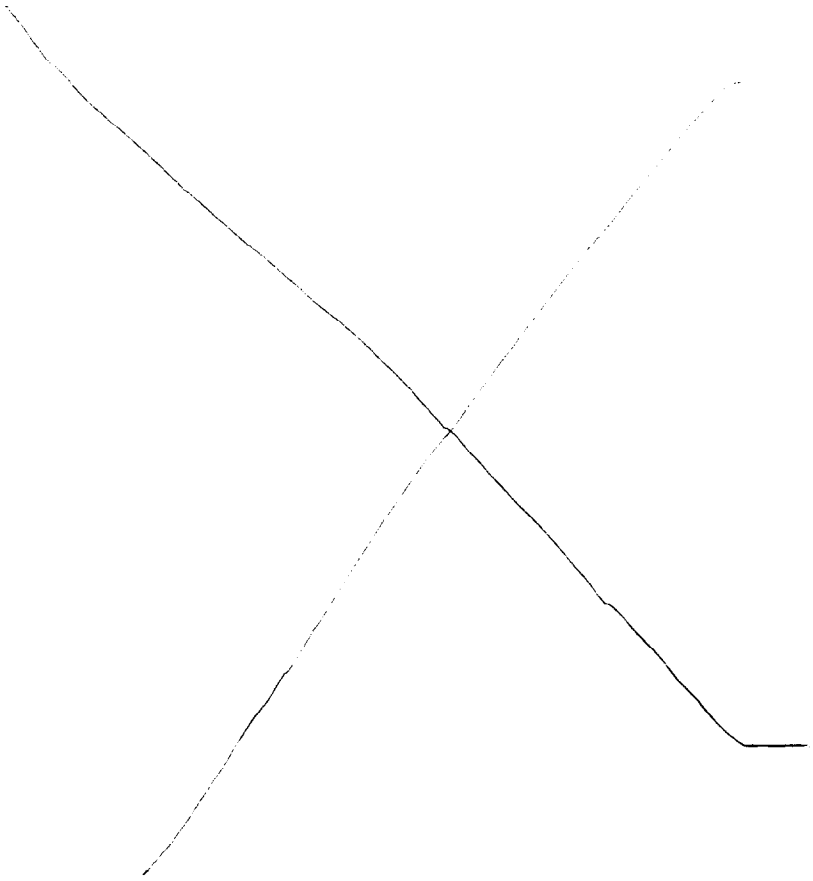
Working Reference Standard lots are qualified and compared to the existing Working Reference Standard with respect to identity, potency, purity and microheterogeneity according to [redacted]ese tests and results are documented on the certificate of analysis [redacted] for each lot qualified. The Reference Standard, once qualified, is placed on a stability protocol. The characterization of the Working Reference Standard encompasses a series of analytical tests to confirm that the structural identity and biological activity is consistent with established criteria set in the Master Specification. MEDI-493 Working Reference Standard material is tested for identity by performing the following comparability tests: SDS-PAGE, reducing IEF and Western blotting for heavy and light chain. Purity of the material is assessed by performing SDS-PAGE, reducing IEF, Western blotting for heavy and light chain and high performance size exclusion chromatography (HPSEC).

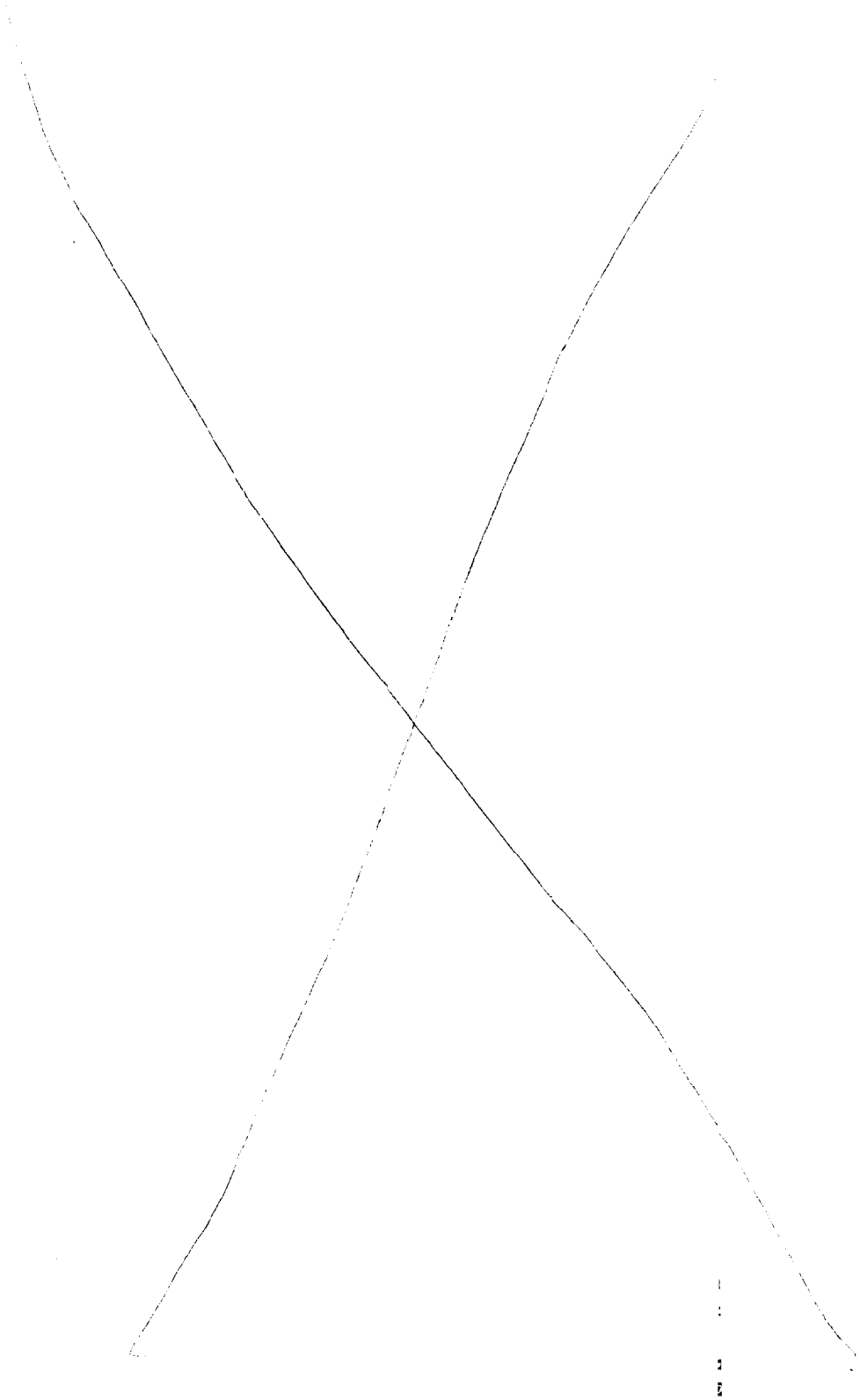
Potency is determined by the ELISA and microneutralization assay. Additional tests to assess microheterogeneity are also performed. This testing includes: carbohydrate composition, carbohydrate profiling, partial light chain and CNBr digest followed by N-terminal sequencing, MALDI-TOF mass spectroscopy, peptide mapping, and oligosaccharide profile analysis.

Comparability

MEDI-493 has consistently shown similar biochemical and functional properties throughout the clinical campaigns. For example, the biological activity assays, ELISA and microneutralization, were within specifications for all lots tested. In addition, identity and purity assays such as SDS-PAGE, Western blotting, reducing IEF, HPSEC, peptide mapping, MALDI-TOF mass spectrometry, and in situ CNBr sequencing have shown consistent results when the clinical lots were compared to each other or Reference Standard.



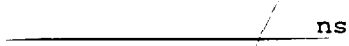




History of Process Changes

(from BLA Section 4.4)

The cell culture and purification processes used for the manufacture of Phase I, II and III clinical material are very similar to the current commercial production. The process modifications made during clinical development of MEDI-493 and the lots produced with those process modifications are summarized in the following sections and in Table 4.4-1. The lots used in the various MEDI-493 clinical studies are summarized in Tables 4.4-2, 4.4-3 and 4.4-4.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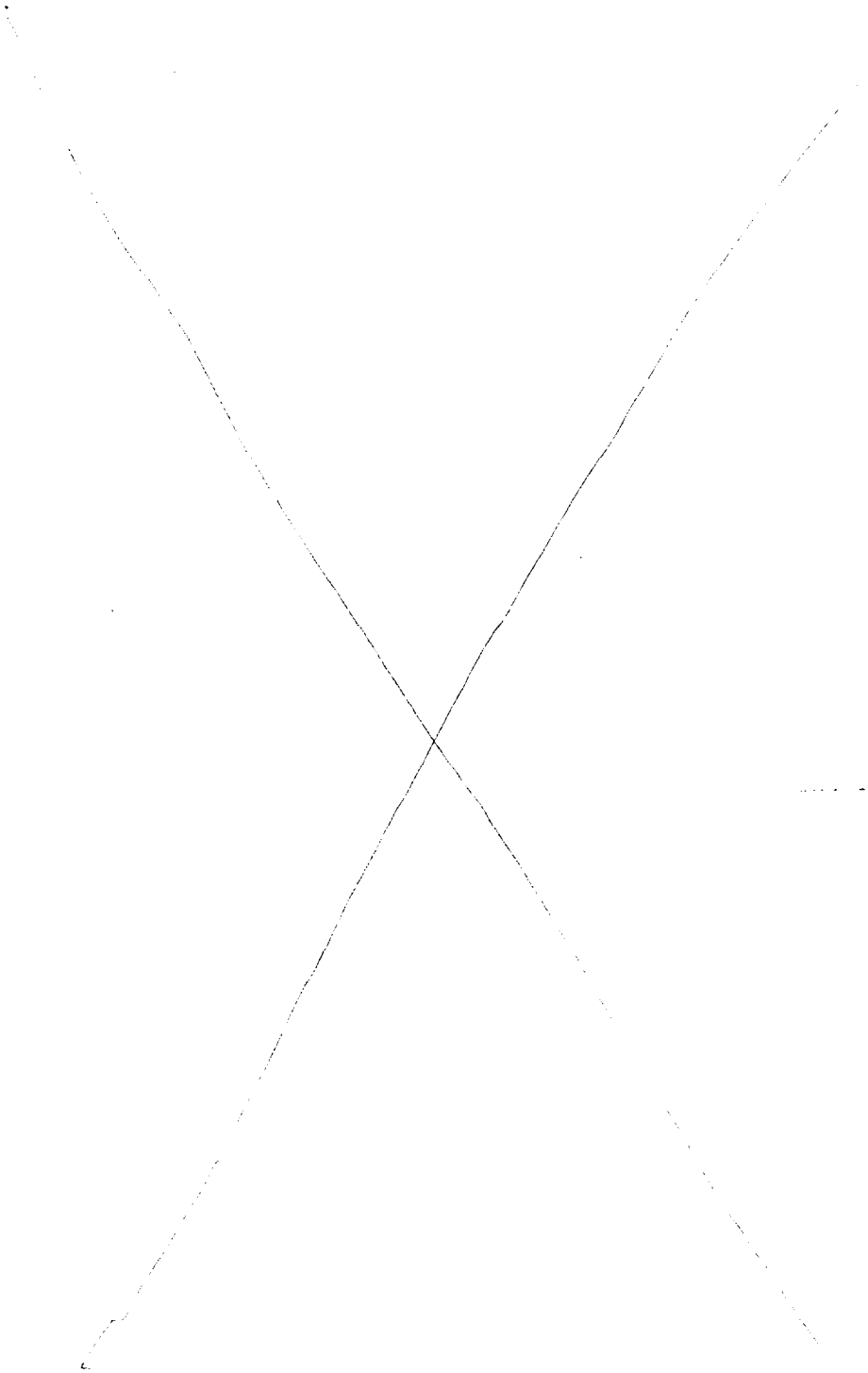

Enviromental Assessment Reports

(Section 4.5 of the BLA)

MEDI-493 is a humanized monoclonal antibody and, as such, is designated as a specified biological. For this reason MedImmune requests an exemption under a categorical exclusion in accordance with 21 CFR Part 25.

Conclusions

(bold type reflects FDA comments and non bold type reflects MedImmune responses)

1)What are the role of Fc functions, such as complement fixation, in the in vivo activity of Palivizumab. MedImmune has performed cotton rat studies of RSV prophylaxis using Fab' and (Fab')2 fragments of Palivizumab stated that the study was done with intranasal delivery of product and demonstrated anti RSV effects without the Fc region (which contains the CHO site as well as Fc functions). **This suggests that complement is not important in the MEDI-493 cotton rat effects. However, Fc and CHO effects on delivery of systemic MEDI-493 to the lung is not evaluted in an intranasal study. Therefore any changes in the product which may effect the Fc region, such a CHO changes, may necessitate further pre-clinical studies on MEDI-493. This was discussed at the inspection**

2)In a study to look for Palivizumab escape mutants,an RSV plaque was recovered from a MEDI-493 treated cotton rat in 100 mcg/ml Palivizumab and grown in 50 mcg/ml Palivizumab(BLA section 7.2.4 vol 28 pg 35). This RSV isolate was found to be sensitive to Palivizumab in the microneutralization assay. What levels of Palivizumab were required for neutralization of this isolate in the plaque reduction or microneutralization assays? In a telecom on with the sponsor, pointed out that the levels of Palivizumab required for neutralization of passaged RSV may be sensitive to nonreplicating viral particles. The nonreplicating viral particles compete for antibody and the numbers of these competed particles decreases with passaging. Therefore the MEDI-493 concentration required for neutralization is not always a useful way of comparing isolate sensitivity in a quantitative manner. **Was this isolate an escape mutant?** submission to the BLA (CBER The sponsor notes that on further review and design of the experiment to evaluate escape mutants in the cotton rat model, the virus from which the resistant plaque was not expanded in antibody as suggested in the BLA. It is possible that this isolate was resistant and then reverted when selective pressure was removed or that it was never resistant to MEDI-493 in the first place.

3) Have clinical isolates from the IMpact study been evaluated for sensitivity to Palivizumab? This would be especially useful with RSV isolates from treated subjects who were hospitalized for RSV infection

discussed the sensitivity of isolates from MEDI-493 treated subjects, in a telecom on with the sponsor regarding phase 4 studies. From the eatment study a number of isolates were evaluated both at baseline and after treatment. At this time, 10 isolates were neutralized by MEDI-493 (3 at baseline and 7 post MEDI-493 treatment). From the IMpact study, out of 7 isolates, 6 have been cultured, 4 are clearly neutralized and 2 are still being evaluated. An earlier summary of this data describing the results from 5 of the IMpact study isolates was submitted to the BLA in CBER

. **What is the likelihood of RSV escape mutants?** In discussion of escape mutant surveillance in the telecom, pointed out the doses of MEDI-493 used reduce lung RSV titers but not nasal titers. This would make passage of an escape mutant less likely since the nasal viruses are the source of infection. **What is the plan for surveillance of RSV sensitivity to Palivizumab?** outlined a plan to evaluate escape mutants or variant viruses resistant to MEDI-493. This would be a surveillance of 4-5 geographic centers with the ability to culture RSV. They would attempt to obtain 10 RSV isolates from each center and would evaluate MEDI-493 microneutralization of these isolates. They would attempt to obtain isolates from MEDI-493 treated subjects with RSV hospitalizations, but were uncertain how many isolates they could recover. They will attempt to capture relevant clinical data and sample in a systematic manner. pointed out the technical difficulty in virus recovery might affect the number of isolates they can recover.In a 6/2/98 submission to the BLA, a proposal for the monitoring of RSV isolates was described. The plan is for 2 years of monitoring with review after that time. **A 3 year follow up with reconsideration of the frequency of monitoring at that time with CBER was suggested on a telecom on** This will be included in the commitment letter.

3) The media used for growth of the cells contains The potential for this to inhibit the growth of mycoplasma has not been evaluated. This may mask a mycoplasma infection of the cell line. On the and a telecom on data on the effect of on mycoplasma were requested. On the telecom, stated that the results of a study evaluating the effect of on mycoplasma growth would not be complete for another 4-5 weeks. A telecom on 6/9/98 discussed this. The sponsor has demonstrated no effect of the media with on the growth of three organisms. Mycoplasma was not evaluated. A plan was faxed to CBER and discussed in the telecom. The study on the effect of on mycoplasma will be included in the commitments.

4) The column used in the phase 3 lots has been removed from manufacturing process. What is the supportive data that the product is unaffected? The three consistency lots have been made without the column based an data submitted to the BLA on . In this submission Table 1 summarizes the average lot release data from clinical lots . The step did not seem to significantly decrease the levels of impurities after the step.

5) In the CBER calculation of viral clearance, we did not count elution (since the elution was different than the manufacturing process)and the step was not counted due to buffer and parameter changes between what was validated for viral clearance (BLA vol 17 pg 130, 136) and used in manufacturing (BLA vol 15 pg 18-27; Edition 004). The column manufacturing parameters need to be adjusted to match the viral validation parameters are a load of and a linear flow rate of

. These issues were raised at the inspection ( ) and formally stated to Medimmune in a telecom c

. The sponsor's commitment to these parameters and to additional viral clearance studies with resin used for cycles and at the end of the resin lifetime was documented in the submission CBER in response to question 1(a) relayed in the telecom. **With the adjustments to the column parameters, the model viruses are cleared by a factor of greater than 3 logs using the present process . Xenotropic retrovirus is cleared by over 6 logs per dose based on the calculations in the following table:**

The variance and data for the column manufacturing parameters were requested in a telecom on the sponsor submitted viral clearance data . The load and flow rates of all lots at were below these new scaled down parameters.

6) Acceptance values for these in process tests in validation of the process are described in BLA Sections 4.2.4.2.1 (fermentation) and 4.2.4.2.1 (purification). What are the critical in process tests for manufacturing and what are their specifications? On a telecom, this question was discussed. In the submission to the BLA, on page 28, a table of provisional in process specifications are provided.

7) The lot release specifications can be narrowed based on Palivizumab manufacturing experience. On t

CBER. The CGE specs included criteria for migration times and > than heavy and light chain. The IEF specs require major and inor bands with band 1 at and band 2 at The specifications for impurities were also narrowed.

All the specifications were lowered except the . The Benzonase specification is much greater than the amount that should be present from the levels described in point number 11 which follows. The testing done here is less sensitive than that done for the clearance. The levels used as specifications here are based on experience with the lot release test. The lot release test for Benzonase would reveal major purification problems rather than accurately quantitating the small amounts of Benzonase present in the product. This test will be discontinued with the remaining impurities testing with appropriate data on column clearance, cleaning and lifetime. **A commitment should be made to validate the new Endonuclease test.**

8) The BLA does not contain sufficient data on column performance (impurity clearances and column cleaning and lifetime data) to warrant removal of the impurity testing. Impurity testing will need to be continued till cleaning validations and clearance validations of the columns are complete. This was conveyed to the sponsor at the inspection and in a telecom on of BLA issues discussed during the inspection. In the submission to the BLA CBER , commitment to this testing was made by MedImmune.

9) Antifoam emulsion is use in the fermentation of MEDI-493. No data has been supplied to demonstrate its removal from the product. In a telecom data for the antifoam removal was requested. In a submission to the BLA on 8 (CBER , information was supplied regarding the antifoam. It is used at 1 ppm concentration on the culture media and is anionic so it is highly unlikely to bind the ion exchange resin in the first purification step. A worst case scenario by the sponsor, assuming a large fraction of the antifoam copurifies with the product, still has it at levels that test negative for mutagenicity in an Ames test. **A commitment to demonstrate clearance of the antifoam was requested on a telecom on .** This was agreed to by the sponsor.

10) The material ill be dealt with as a separate submission) material have different lyophilization parameters tha- the phase 3 material (lyophilized at . There were two major differences noted on inspection. One is that the the primary drying was at at econd is that the the ramp time and primary drying time were longer at han at MedImmune wishes to have a 24 month expiration date. This will depend on the assessment of the lyophilization differences between the phase 3 clinical lots and the consistency lots. On 5/15/98 a submission by MedImmune (CBER discussed the differences in lyophilization. Of note in this submission is that one of the 3 clinical lots (lyophilized at with 18 month stability data) had a primary drying temperature of similar to that of the consistency lots lyophilized at This lot, similar in its stability testing results, incuding initial moisture and 12 month moisture testing, to the lots with a primary drying temperature of -10°C. **There were still differences in the primary drying and ramp rates between . The ramp rate at as and the total primary drying time was and at the ramp rate is 19-26° C/hr with a total drying time of The time that the product temperature was at the primary drying temperature was similar between the two facilities: hrs at hrs at This lyophilization data is being reviewed by as a consultant. He felt that the two lyophilizations were different and stability data from would need to be evaluated.** In a submission on June 8th 1998, additional stability data was submitted. This data includes 6 month drug substance stability at 2-8°C and 20-24°C on the three consistency lots in gs(pages 8-11 of the submission) and 6 month stability of drug product (lyophilized at at 2-8°C and 20-24°C on the three consistency lots (pages 28-30 of the submission). The moisture testing of the drug product, at 2-8°C, initially was and at 6 months was The moisture on the three phase 3 lots with 18 month stability (lyophilized at went from 0.8-0.9% initially to at 12 months. The moisture from an earlier lyophilized lot , which has 24 months of stability data varied from . The material is not gaining moisture at a more rapid rate than the material. Data from the lyophilization lot reviewed by indicates thare was no meltback in the lyophilized s. Because the data from the material is comparable to the material at 6 months of stability and MedImmune will be continuing to follow stability on the consistency lots (~6 months ahead of the marketed lots), we will accept the use of the material for stability and agree to a expiration date. This depends on the answering of some remaining questions regarding the lyophilization validation submitted on 6/3/98 (CBER)

11) In some studies [redacted] has been associated with chromosomal effects on CHO cells. Only in one study was this chromosomal effect seen in CHO cells that were not physically disrupted by ultrasound or hypertonic glycerol and this occurred at a dose of [redacted] g/ml. Evidence for the removal of [redacted] was requested in a telecom on [redacted]. During the inspection of the [redacted] on [redacted], the removal of [redacted] was further discussed with [redacted] er. Testing of the final reconstituted samples allows a 10 fold greater sensitivity. Three samples were tested and the results of the testing are between the LOD and the LOQ of the samples. The LOQ is [redacted] So the most a 100 mg dose would have is [redacted] units (0.7 ng/100mg or 7 parts per billion). This is similar to the levels demonstrated in the [redacted] clearance study in the BLA. Effects on chromosomes from Benzonase in the ng/ml are only seen in CHO cells that are permeabilized.

Medimmune has committed to demonstrate additional clearance of benzonase to increase the margin of safety. On [redacted] MedImmune submitted data from a new assay for [redacted], the [redacted] This assay is 1400 times more sensitive than the previously used assay. In lots purified with the [redacted], the maximal amount of benzonase activity detected per 100 mg of product in the final vial is 0.011 U or ng. This is a greater than 50 fold improvement in the safety margin. Based on MedImmune's calculations in the [redacted] ission, there is a 3 log safety margin based on the dose in which the CHO cell effects were seen.

12) The specifications for the comparability protocol are very broad compared to the experience of the sponsor. For example, the peak ratio specifications for oligosaccharide structural analysis [redacted] are much broader than the data from production lots. The comparability protocol gives an example of a 10x increase in scale requiring comparability. The comparability protocol as in the BLA is not acceptable until justification for the specifications are submitted. Until that time point comparability questions will need to be discussed with CBER on a case by case basis. On a [redacted] telecom it was made clear to the sponsor that the specifications in the comparability protocol are too broad and that the protocol will need to be revised before it can be operative. The sponsor understood and expressed interest in revising the protocol.

13) The [redacted] onsistency lots all fall within the comparability specifications set by the sponsor. These specifications may be too broad (see comments on the comparability protocol above). There were no actual chromatographs included with the comparability data. These were requested in a telecom on 2/4/98. Additional comparability data, which includes [redacted] was submitted in tabular form on [redacted] id chromatographs of the peptide mapping and oligosaccharide analysis were submitted on 2 [redacted] hromatographs of the peptide mapping and oligosaccharide analysis were submitted in a clearer form on [redacted] **The test results need to be directly compared to clinical lot results. The BLA or submission [redacted] chromatographs that can be overlayed or examples of side by side gels with the**

comparability data. Ideally side by side analysis of the three consistency lots and three clinical phase 3 lots should be submitted to the BLA. These were requested on [redacted] telecoms. Side by side data of IEF gels and overlays of the peptide mapping and oligosaccharide analysis were submitted on [redacted] n submission CBER [redacted] consistency, phase 3 clinical and [redacted] ots were compared. Since with MW markers only 8 lanes were available on the gels, a minimum of 2 lots of each source were run together on each gel. The [redacted] submissio[redacted] resolved questions regarding minor differences in the peptide mapping peaks seen a[redacted] tes. **The comparability data submitted show greater similarity than the broad specifications in the comparability protocol and are satisfactory.**

Recommendations

The data submitted in this application support the conclusion that the manufacture of Palivizumab (Synagis™) is well controlled and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents in a way that meets or exceeds the parameters recommended by the FDA. The conditions used in manufacturing have been validated and a consistent product is produced from different production runs. The biochemical and biophysical properties of the product have been maintained throughout the manufacturing history. I recommend approval of this product for human use if the following issues are resolved:

1) A letter of clinical and manufacturing agreements which satisfies the FDA review team.

2) Final resolution of the package insert contents.

3) Resolution of the validated conditions for the product lyophilization.